

Appln No.: 09/601,644

Amendment Dated: March 3, 2005

Reply to Office Action of December 3, 2004

#### REMARKS/ARGUMENTS

This is in response to the Office Action mailed December 3, 2004 for the above-captioned application. Reconsideration and further examination are respectfully requested.

The Examiner made the restriction requirement final, and indicated that claims 17-42 were withdrawn from consideration. As a first matter, Applicants submit that this restriction as it applies to claim 42 is in error, since claim 42 depends on claim 1. Furthermore, the basis for the restriction requirement is an alleged anticipation of claim 1 by cited references. As is demonstrated below, there is no anticipation in fact. Accordingly, there is unity of invention and all of the claims should be considered in this application. Reconsideration is again requested.

Applicants have amended the specification to provide sequence listing numbers in Table 1, 2 and 3. A new sequence listing has been filed electronically, and a paper copy is enclosed. The undersigned certifies that the paper copy enclosed herewith is the same as the copy of the sequence listing filed electronically.

Applicants have also electronically filed an Information Disclosure Statement for his application, listing US Patent No. 5,552,144. Consideration of this IDS, and entry of the patent into the record is requested. The fee has been paid with the electronic disclosure statement.

Claims 1-16 stand rejected under 35 USC § 112, second paragraph, as indefinite. These claims have been amended to make the corrections suggested by the Examiner.

The Examiner rejected claims 1-3, 5, 8-13 and 16 as anticipated by Jackson et al. In support of this rejection, the Examiner reproduces the language of claim 1, and then cites to certain teachings in the Jackson paper. No analysis is provided as to how these teachings meet the language of the claims, however.

The present claims require as screening step in which "the variant forms of the heteromeric protein toxin of said library [are screened] against a population of screening cells by isolating clones or pools of clones producing said variant forms of the heteromeric protein toxin, treating preparations of said population of screening cells with variant forms of the heteromeric protein toxin produced by the isolated clones or pools of clones, and **selecting a cytotoxic mutant protein or pool of cytotoxic mutant proteins that inhibits or kills said population of screening cells to a greater extent than the wild-type cytotoxic mutant protein.**" The Examiner has not indicated how this limitation is met by the Jackson reference. In Jackson, there are no proteins that are shown to kill or inhibit cells to a greater extent than the wild-type and thus there can be no selection of such proteins or copying of such proteins. Thus, Jackson does not anticipate the claimed invention.

Appln No.: 09/601,644

Amendment Dated: March 3, 2005

Reply to Office Action of December 3, 2004

It is noted that the Examiner refers to the disclosure of insertion of amber mutations into the sequence, and the effect of different types of suppressor systems in host organisms. This is not a comparison of mutant to wild type, however, but a comparison of mutant in host 1 to the same mutant in host 2. Indeed, the activity reported in the cited Jackson Table is either the same as or less than the wild-type activity (pEW3.0). Thus, this comparison is not relevant to the present claims, and does not provide an anticipatory disclosure.

The Examiner also rejected claims 1-3, 5, 8-13 and 16 as anticipated by Tyrell et al. In the Tyrell paper a mutant is reported that has higher cytotoxicity than the parent toxin (VTE). However, the mutants were made by specific introduction of mutations, not by creating a library, and there is no screening for higher activity mutants from a library of mutants. Thus, the teaching of Tyrell does not include each and every element of the claimed method, making an anticipation rejection improper.

The Examiner rejected claims 1, 4, 6, 7, and 13-15 as obvious over Jackson or Tyrell in combination with various secondary references. Applicants respectfully traverse this rejection. The present application relates to making mutant forms of a cytotoxic protein that have characteristics different from the wild-type protein, and which are more effective against the screening cells than the wild-type protein. In the preferred embodiment of claim 42, the screening cells are insensitive to wild-type protein such that even very low mutants that act with low efficacy can be identified in comparison, but any screening cell population against which wild-type protein is a limited efficacy (i.e., where there is room to see an increase in efficacy) can be used. The purpose and intent of the two primary references is very different, making any modification of them to arrive at an obviousness rejection suspect.

The Jackson paper has as its focus the determination of the location of the binding site on Shiga and Shiga-like toxin that is responsible for their toxicity to normal targets. The paper does not relate to determination of mutants with different specificity, and discloses no method for making such mutants. The Tyrell reference relates to very specific mutations in the binding subunit of Verotoxins to change their binding specificity. As noted above, however, the Tyrell reference does not disclose the basic elements of the present invention, and so combinations of Tyrell and other references also fail to arrive at the claimed invention.

Furthermore, it is well established that in order to make an obviousness rejection "citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious." *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988). In this case, even if the teachings of the primary references were closer to the claimed invention, the rejections under 35 USC § 103 would still be insufficient because combination of references is improper.

Appln No.: 09/601,644

Amendment Dated: March 3, 2005

Reply to Office Action of December 3, 2004

With respect to the limitation of claim 4, namely that "said library comprises yeast or yeast supernatants containing said variant protein toxins" the Examiner asserts modifying the primary reference to use a yeast library would have been obvious because a yeast library was known from the Cheng reference. The Examiner has not said where in the teachings of the primary references this modification would be made, or what features of the references, as opposed to the terms of the present claims, would have suggested such a modification. As the courts has stated, "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 140, 231 USPQ 644, 647 (Fed. Cir. 1986) (citing *ACS Hosp. Syss., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). "[T]he factual inquiry whether to combine references must be thorough and searching." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Here, no factual inquiry is demonstrated by the Examiner, and thus no valid *prima facie* rejection.

With respect to claim 6, which recites the use of a combinatorial cassette, the Examiner cites a secondary reference, Reidhaar-Olson as teaching "random mutagenesis of protein sequences using cassette mutagenesis." Again, the rejection is nothing more than an assertion, without reasoning or support, that using this known method in combination with the primary reference would have been obvious. This is not sufficient, particularly since neither primary reference uses random mutagenesis.

Claims 1 and 7 are rejected as obvious over Jackson or Tyrell in view of Nickoloff. Nickoloff is cited merely for disclosure of a mutagenesis technique. Thus, Nickoloff does not overcome the fundamental deficiencies of the Jackson and Tyrell references, and this rejection should therefore be withdrawn.

Finally, the rejection of claims 13-15 as obvious over Jackson or Tyrell in view of Frankel is lacking in any motivation to combine the references. Claims 13-15 relate to the use of tumour cells, particularly breast cancer cells such as SKBr-3 and CAMA-1 as the screening population. Frankel teaches the breast-cancer specific monoclonal antibodies conjugated to ricin as a cytotoxic agent, and to the use of these compositions in killing breast cancer cells. This patent has nothing to do with the development of toxins, but rather with the development of antibodies. As such, it is non-analogous art that is not properly relied upon. There is no indication that breast cancer cell lines should or could be used in testing cytotoxic mutant proteins and no reason outside the present disclosure to make the proposed combination.

Appln No.: 09/601,644

Amendment Dated: March 3, 2005

Reply to Office Action of December 3, 2004

For these reasons, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

*Marina T Larson*

Marina T. Larson, Ph.D  
Attorney/Agent for Applicant(s)  
Reg. No. 32038

(970) 468 6600

Page 14 of 14